

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION

(PCT Rule 66)

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Applicant's or agent's file reference

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REPLY DUE

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International application No.

PCT/US98/19494

International filing date (day/month/year)

18/09/1998

Priority date (day/month/year)

19/09/1997

International Patent Classification (IPC) or both national classification and IPC

C12N15/53

DI Dec. 14, 1999

Applicant

PROMEGA CORPORATION et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain document cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary

examination report must be established according to Rule 69.2 is: 19/01/2000.

Schwegman, Lundberg,
Woessner & Kluth. P.A.

SEP 2 0 1999

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I. Basis of the opinion

1. This opinion has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, pages:

1-76 as originally filed

Claims, No.:

1-38 with telefax of 16/04/1999

Drawings, sheets:

1/59-59/59 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 2, 4, 7, 8, 10, 13-15, 17-24, 38,

because:

- ☒ the said international application, or the said claims Nos. 2, 4, 7, 8, 10, 13, 24 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 14, 15, 17-23, 38.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims
Inventive step (IS)	Claims
Industrial applicability (IA)	Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Citations

The documents mentioned in this Written Opinion are numbered as in the International Search Report dated 19.03.99, i.e. D1 corresponds to the first document of the search report etc.

Re ITEM I (Basis of the opinion)

- 1 The amended claims 1, 3, 5, 6, 9, 11, 12 and 14-38 filed with telefax of 16.04.99 can be regarded as meeting the requirements of Art. 34(2)(b) PCT.
- 2 The amended claims 2, 4, 7, 8, 10 and 13 filed with telefax of 16.04.99 contain subject-matter which extends beyond the disclosure in the international application as filed and therefore contravene Art. 19(2) PCT. The following amendments are not allowable:
 - 2.1 Claims 2 and 4: no basis could be found for the features "five/ten hours in an aqueous solution *at about 50°C*". The expression "*at about 50°C*" renders the scope of protection broader than "*at 50°C*" (cf. p. 2, l. 11 and p. 4, l. 13).
 - 2.2 Claims 7 and 8: no basis could be found for the features "six hours/two days in an aqueous solution *at about 60°C*". The expression "*at about 60°C*" renders the scope of protection broader than "*at 60°C*" (cf. p. 4, l. 22 and p. 4, l. 24-25).
 - 2.3 No basis can be found for the subject-matter of claim 10 ("*at least 90%* after six weeks at 22°C") (cf. p. 4, l. 26: "5% loss over 6 weeks").
 - 2.4 No basis can be found for the subject-matter of claim 13 ("wherein each mutation changes the native amino acid to a consensus amino acid").
 - 2.5 No basis can be found for the subject-matter of claim 24 ("*RNA which encodes a beetle luciferase*").

According to Rule 70.2(c) PCT, this opinion has been established as if some of the amendments had not been made, since they have been considered to go beyond the disclosure as filed. Therefore, under Rule 70.2(c) PCT (see also **ITEM III**) examination is being carried out on the basis of claims 1, 3, 5, 6, 9, 11, 12, 14-23 and 25-38 filed with telefax of 16.04.99 but not for the subject-matter of new claims 2, 4, 7, 8, 10, 13 and 24 for which no basis could be found in the original claims, description or drawings.

Re ITEM III (Non-establishment of opinion)

- 1 No search report has been established for the subject-matter of original claims 16, 21 and 22. Thus, preliminary examination has not been carried out for the sequences defined in new claims 14, 15, 17 and 38; said claims correspond to original claims 16, 21 and 22 (Rule 66.1(e) PCT). Consequently, examination has not been carried out for the subject-matter of claims 18-23 and 38; said claims refer to the sequences defined in new claims 14, 15, 17 and 38 for which an International Search Report has not been established (also cf. PCT Guidelines VI-8.4, last sentence).
- 2 For the reasons stated under **ITEM I, 2**, no examination has been carried out for the subject-matter of new claims 2, 4, 7, 8, 10, 13 and 24.
- 3 In summary, examination has been restricted to the subject-matter of claims 1, 3, 5, 6, 9, 11, 12 and 34-37 (completely) and claims 16 and 25-33 (partially) in so far as they refer to the subject-matter of claims 1, 3, 5, 6, 9, 11 and 12.

Re ITEM V (Novelty, inventive step, industrial applicability)

1 Summary of the present application

The present application is related to thermostable beetle luciferases and a process for the identification of thermostable beetle luciferases.

2 Novelty (Art. 33(2) PCT)

- 2.1 The subject-matter of claims 1, 3, 5, 6, 9, 11, 12 and 34-37 (completely) and claims 16 and 25-33 (partially) has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel.

D1 discloses a beetle (firefly) luciferase which remains 65% or more of its activity after 60 min at 50°C (D1, p. 4, l. 30-31). **D2** discloses a beetle (firefly) luciferase with a half life of 30 min at 43.5°C in 50mM potassium phosphate buffer pH 7.8 (D2, p. 12, Example 2). **D3** discloses a beetle (firefly) luciferase with a half life of 12 min at 40°C (see Table 1 of D3). However, said documents do not disclose a beetle luciferase with a half life of two hours at 50°C or a DNA which encodes for such a luciferase (independent claims 1 and 16) (attention is drawn to **ITEM VIII, 1**).

- 2.2 Uses according claims 25-32, viz. of a synthetic luciferase with a half life of two hours at 50°C, and the hybrid protein of claim 33 have also not been disclosed in the available prior art documents and can therefore be regarded as novel.
- 2.3 Also the method according to independent claim 34 wherein recursive mutagenesis and selection ("directed evolution", cf. p. 5, l. 29-p. 6, l. 8) is applied to prepare a mutant beetle luciferase with a half life of two hours at 50°C has not been disclosed in the available prior art.

3 Inventive step (Art. 33(3) PCT)

The subject-matter of claims 1, 3, 5, 6, 9, 11, 12 and 34-37 (completely) and claims 16 and 25-33 (partially) cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Art. 33(3) PCT.

4 Industrial applicability (Art. 33(4) PCT)

Claims 1, 3, 5, 6, 9, 11, 12, 16 and 25-37 meet the criteria as set forth by Art. 33(4) PCT.

Re ITEM VI (Certain published documents (Rule 70.10))

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-98 46729	22.10.98	07.04.98	11.04.97

Said document has been published after the filing date of the present application and does therefore not constitute prior art in the meaning of Rule 64(1)(b) PCT. However, **D6** claims an earlier priority than the present application and will therefore become of relevance for the novelty of the claimed subject-matter during regional phase examination.

Re ITEM VII (Certain defects in the international application)

The present application contains such a high number of independent claims (17 out of 38!) that the application as a whole lacks conciseness (Rule 6.1(a) PCT). Independent claims which are directed to the same category shall be made dependent upon each other to meet the requirements of Art. 6 PCT in combination with Rule 6.4 PCT.

For example, independent claims 25-28 are all directed to "the use of the synthetic luciferase".

Re ITEM VIII (Certain observations on the international application)

- 1 Concerning claims 1, 3, 5, 6, 9, 11, 12, 33 (protein) and claim 16 (DNA), the Applicant is reminded that Rule 6.3(a) PCT requires that the matter for which protection is sought be defined in terms of technical features of the invention (also cf. PCT Guidelines III-4.4, as in force from 09.10.98). A peptide/DNA is a chemical compound which can be clearly and unambiguously defined by its chemical structure, i.e., its amino/nucleic acid sequence. Reference to the appropriate sequence should therefore be given in said claims to meet the requirements of Art. 6 PCT.

The IPEA is of the opinion that the definition of the half life at a certain temperature and time is by no means a sufficient way to define a protein. As a general rule, the characterization of a chemical compound solely by its parameters is not allowable (cf. PCT Guidelines III-4.7a). Attention is drawn to the fact that none of the specific sequences defined in Figures 22-47 have been searched by the ISA (see also **ITEM III, 1**).

- 2 Any claim directly or indirectly depending on the unclear subject-matter of claims 1, 3, 5, 6, 9, 11, 12 or 16 does also not satisfy the requirements of Art. 6 PCT.

Should the Applicant file a new set of claims, he is requested to indicate with his reply where there is a basis for each amendment in the application as originally filed. If the Applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

The Applicant's attention is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the disclosure in the international application as filed (Art. 34(2)(b) PCT).